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MAJOR ARTICLE

Virologic Failure and Human Immunodeficiency Virus Drug Resistance in Rural Cameroon With Regard to the UNAIDS 90-90-90 Treatment Targets

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Background. In rural Africa, data on virologic effectiveness of antiretroviral treatment (ART) are not sufficient to assess the gap with the UNAIDS 90-90-90 treatment targets. We investigated the prevalences of unsuppressed viral load and antiretroviral drug resistance and the profile of genotypic resistance mutations among patients routinely treated in rural Cameroon.

Methods. A cross-sectional study was performed in 2013–2014 among patients ≥15 years and on first-line ART for ≥6 months in a district hospital. Patients were offered free access to human immunodeficiency virus viral load testing. Genotypic drug resistance testing was done when the viral load was >1000 copies/mL. Multivariate logistic regression models were used to assess the relationship of unsuppressed viral load or antiretroviral drug resistance with sociodemographic and medical characteristics.

Results. Of 407 patients (women 74.9%, median age 41.8 years, median time on ART 29.2 months), 96 (23.6%; 95% confidence interval [CI], 19.5–28.0) had unsuppressed viral load and 74 (18.2%; 95% CI, 14.6–22.3) had antiretroviral drug resistance. The prevalences of unsuppressed viral load and resistance increased with time on ART, from 12.0% and 8.0% in the 6- to 12-month group to 31.3% and 27.1% in the >72-month group, respectively. All 74 patients with antiretroviral drug resistance were resistant to nonnucleoside reverse-transcriptase inhibitors, and 57 of them were also resistant to nucleoside reverse-transcriptase inhibitors.

Conclusions. Our estimations were among the highest observed in the west and central African region. The proportion of patients with virologic failure should be divided at least by 2 to reach the UNAIDS 90-90-90 treatment targets.

Keywords. Africa; antiretroviral; resistance; treatment; virologic failure.

Ending the acquired immune deficiency syndrome (AIDS) epidemic by 2030 is the new goal endorsed by the global community [1]. To achieve this goal, the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued a strategy in which antiretroviral therapy (ART) is a key element [2]. This strategy aims that, by 2020, 90% of all people living with human immunodeficiency virus (HIV) will know their HIV serostatus, 90% of all people with diagnosed HIV infection will receive sustained ART, and 90% of all people receiving ART will have viral suppression (90-90-90 treatment targets). By 2030, the targets are 95%-95%-95%.

Western and central Africa is the second most affected region with 6.5 million people living with HIV, but the rate of ART coverage in this region is one of the lowest (28% in 2015) worldwide [3]. Furthermore, the assessment of virologic effectiveness remains a challenge because most patients are still treated without viral load monitoring, especially in rural settings.

In Cameroon, access to ART has been decentralized to district hospitals throughout the country since 2005 [4]. Viral load measurement is recommended 6 months after ART initiation and then once a year by the national AIDS programme [5]. However, this test is seldom performed because it is only available in major cities such as Yaoundé and Douala (the political and economic capitals, respectively) and its cost is supported by the patients [6]. Whereas virologic outcomes among patients receiving ART in urban areas have been widely studied since the beginning of ART use and scale-up in 2000 [7–12], data in rural districts are insufficient to assess the gap with the 90-90-90 treatment targets. Therefore, we investigated (1) the prevalences of unsuppressed viral load and antiretroviral drug resistance and (2) the profile of genotypic resistance mutations among patients routinely treated in a rural district.

METHODS

Study Design

A cross-sectional study was performed between January 2013 and January 2014 among patients who received first-line ART

Received 20 July 2016; editorial decision 18 October 2016; accepted 27 October 2016.

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DOI:

in the Mfou district hospital, which is located approximately 30 km to the south of Yaoundé. In this hospital, access to first-line ART has been available since 2005. Antiretroviral regimen included 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus 1 non-NRTI (NNRTI). Patients requiring second-line ART were transferred-out to a reference HIV clinic in Yaoundé. Demographic and medical data were routinely recorded by social workers and physicians in individual paper medical charts and then entered by a data clerk in an electronic database (ESOPE, Epiconcept, France). Patients were eligible for the study if they were 15 years or older and had started ART since at least 6 months. Eligible patients were offered free access to HIV viral load testing and, if necessary, to antiretroviral drug resistance testing when they attended routine medical visits or by phone calls. Patients with resistance had access to second-line ART. The National Ethics Committee of Cameroon approved the study. Informed consent was obtained for each included patient.

Laboratory Testing

Whole blood samples were collected from included patients attending the Mfou District Hospital and transported within 6 hours to Yaoundé to the reference HIV laboratory of Institut de Recherche pour le Développement/Centre de Recherche sur les Maladies Emergentes et Ré-émergentes, which is accredited by the World Health Organization (WHO) for HIV drug resistance testing. After centrifugation, plasma aliquots were stored at −20°C for further analyses. The HIV-1 groups were identified with an in-house enzyme-linked immunosorbent assay using V3-loop peptides from HIV-1 groups M, N, O, and P [13]. Human immunodeficiency virus-1 ribonucleic acid (RNA) was extracted automatically from 140 µL of plasma (QIAcube; QIAGEN, Courtaboeuf, France), and viral load was measured using the HIV Generic Viral Load assay (Biocentric, Bandol, France). Genotypic drug resistance testing was done using an in-house protocol, which amplifies the protease and reverse-transcriptase regions in a single *pol* gene fragment (~1300 base pairs) when the viral load was >1000 copies/mL [14]. To increase sensitivity of polymerase chain reaction amplification on samples with viral load between 300 and 1000 copies/mL, HIV-1 RNA extraction was performed from 500 µL of plasma and the reverse-transcriptase region was amplified as a separate fragment. Polymerase chain reaction products were directly sequenced using BigDye Terminator version 3.1 Cycle Sequencing kit (Applied Biosystems, Carlsbad, CA). All sequences were checked for quality assurance analysis using the HIVdb Program (http://sierra2.stanford.edu/sierra/servlet/JSierra) before further analyses. Relevant drug resistance mutations were identified and interpreted using the Agence Nationale de Recherches sur le Sida-V25 interpretation rule (www.hivfrenchresistance.org/2015/Algo-2015.pdf). Human immunodeficiency virus-1 subtypes and recombinant forms were identified (1) with phylogenetic tree analysis using the PhyML method [15] and (2) with breakpoint analysis for selected samples using SimPlot software-version 3.5.1.0.

Statistical Analysis

Unsuppressed viral load was defined as viral load >1000 copies/mL (WHO-recommended threshold), and antiretroviral drug resistance was defined as the presence of a genotypic resistance to at least 1 antiretroviral drug. Individual characteristics were compared between included patients and nonincluded patients using the χ^2 test for the categorical variables and the Mann-Whitney test for the continuous variables. Multivariate logistic regression models were used to assess the relationship of unsuppressed viral load or antiretroviral drug resistance with sociodemographic and medical characteristics. Gender (women versus men), age (>35 versus ≤35 years), baseline CD4 cell count (≥100 versus <100 cells/µL), and time on ART (continuous variable) were forced in the multivariate analyses. Time on ART was computed as the number of years between initiation of ART and viral load measurement. Variables associated with outcomes with a *P* value <.25 in univariate analyses were entered into the complete multivariate models. A manual downward elimination procedure was then used to determine the final models. The goodness-of-fit of models were assessed using the conditional Bayesian Information Criterion. All analyses were performed using STATA 13.1 software (StataCorp, College Station, TX).

RESULTS

Patients' Characteristics

Of 1120 patients who had received first-line ART in the Mfou District Hospital, 702 (62.7%) were eligible for the study (Figure 1). Most patients who were not eligible had received ART for less than 6 months (55.0%), and the remaining either died (32.5%), transferred-out (9.6%), or were less than 15 years (2.9%). Of eligible patients, 407 (58.0%) were included. More than two thirds of patients who were eligible but were not included could not be reached because they did not come to routine medical visit nor answer phone calls.

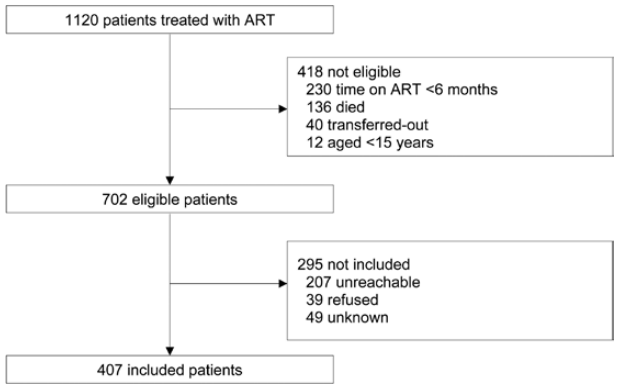

Figure 1. Study flowchart. ART, antiretroviral therapy.

Of included patients, three quarters were women (Table 1). The median age was 41.8 years (interquartile range [IQR], 35.5–48.8). Most patients had started ART at an advanced stage of HIV disease (74.6% at WHO stage 3 and 6.1% at stage 4). The median baseline CD4 cell count was 170 cells/μL (IQR, 95–246) among 341 patients (83.8%) with available data. Most characteristics were comparable between included patients and nonincluded patients, but the former had a slightly higher hemoglobin level (median, 10.2 versus 9.9 g/dL) and had started ART a little earlier (~5 months).

Median time on ART was 2.4 years (IQR, 1.3–4.1; range, 0.5–8.1). Antiretroviral regimen included zidovudine (ZDV), tenofovir disoproxil fumarate (TDF), or stavudine (d4T) + lamivudine (3TC) + efavirenz (EFV) or nevirapine (NVP), with different distributions of regimen between ART initiation and the time of the study (Figure 2). Treatment had been changed because of toxicity or drug stock-out once in 33.4% of patients, twice in 10.7%, 3 times in 2.6%, and 4 times in 0.8%. Antiretroviral therapy changes occurred after a median time of 17.3 months (IQR, 7.4–29.9).

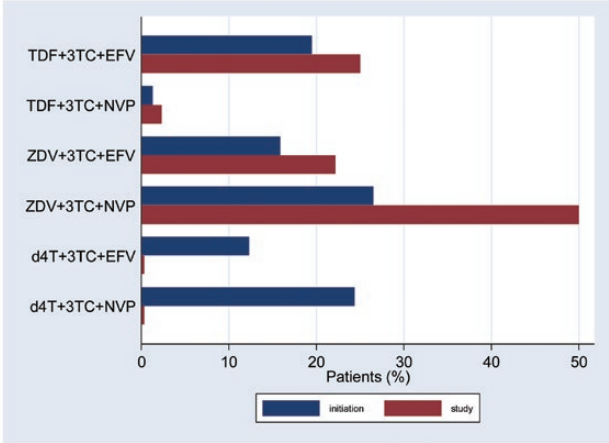

Figure 2. Antiretroviral regimen at treatment initiation and at the time of the study. d4T, stavudine; EFV, efavirenz; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine; 3TC, lamivudine.

Virologic Outcomes

Serotyping was successful for 390 patients and identified 389 infections with HIV-1 group M strains and 1 with a HIV-1 group O strain. However, the genotyping of the latter sample revealed a CRF02_AG strain, suggesting a dual infection or an infection with an O/M recombinant strain.

One hundred twenty patients (29.5%) had a viral load >300 copies/mL. Of them, 96 had >1000 copies/mL, giving a prevalence of unsuppressed viral load of 23.6% (95% confidence interval [CI], 19.5–28.0). Genotyping was successful for 108 patients. Viral strains belonged to non-B subtypes (A, A3, D, F1, and G; 11% of cases), CRF02_AG (65%), other CRFs (CRF01_AE, CRF09_cpx, CRF11_cpx, CRF18_cpx, CRF22_01A1, CRF25_cpx, CRF37_cpx; 12%), and unique recombinant forms (12%).

Table 1. Baseline Characteristics of Patients

	Included (n = 407)			Nonincluded (n = 295)			
	N	n (%) or median (IQR)		N	n (%) or median (IQR)		*P*
Gender							
Women	407	305	(74.9%)	295	216	(73.2%)	.607
Men		102	(25.1%)		79	(26.8%)	
Age (years)	406	41.8	(35.5–48.8)	291	41.4	(33.8–48.9)	.347
School educational level							
Never attended school	320	13	(4.1%)	187	12	(6.4%)	.216
Primary		103	(32.2%)		66	(35.3%)	
Secondary		180	(56.2%)		102	(54.6%)	
Higher		24	(7.5%)		7	(3.7%)	
Marital status							
Single or divorced	392	196	(50.0%)	290	140	(48.3%)	.140
Married or cohabiting		148	(37.8%)		126	(43.5%)	0
Widowed		48	(12.2%)		24	(8.3%)	
Bodyweight (kg)	371	58	(50–65)	280	56	(50–64)	.222
WHO stage							
1	394	35	(8.9%)	295	16	(5.4%)	.335
2		41	(10. 4%)		28	(9.5%)	
3		294	(74.6%)		230	(78.0%)	
4		24	(6.1%)		21	(7.1%)	
CD4 cell count (cells/μL)	341	170	(95–246)	241	186	(88–275)	.375
Hemoglobin (g/dL)	353	10.2	(9.0–11.7)	254	9.9	(8.4–11.2)	.009
Date of ART initiation	407	October 30, 2010	March 2, 2009–January 16, 2012	293	March 16, 2011	Marche 22, 2009–May 24, 2012	.015

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; WHO, World Health Organization.

Of the 96 patients with viral load >1000 copies/mL, 74 (77.1%) had antiretroviral drug resistance. No patient with a viral load between 300 and 1000 copies/mL and successful genotyping (12 of 24) had resistance. The overall prevalence of resistance was 18.2% (95% CI, 14.6–22.3). Median viral load was 4.6 $\log_{10}$ copies/mL (IQR, 3.9–5.8) among patients with unsuppressed viral load but without resistance and 5.1 $\log_{10}$ copies/mL (IQR, 4.5–5.7) among those with resistance.

The prevalences of unsuppressed viral load and antiretroviral drug resistance increased with time on ART (Table 2). This finding was confirmed by the logistic regression analyses, even after adjustment for gender, age, and baseline CD4 cell count (adjusted odds ratio [aOR] = 1.17, 95% CI = 1.01–1.34, $P = .033$ and aOR = 1.23, 95% CI = 1.05–1.43, $P = .009$, respectively; Table 3). By contrast, the prevalences of both outcomes were lower among patients who had started ART with a CD4 cell count ≥100 cells/μL than among those with <100 CD4 cells/μL (aOR = 0.58, 95% = CI 0.34–0.99, $P = .047$ and aOR = 0.52, 95% = CI 0.29–0.94, $P = .029$, respectively). Finally, the prevalences did not differ according to gender, age, school educational level, marital status, and baseline body weight, WHO stage, or hemoglobin level.

All 74 patients with antiretroviral drug resistance were resistant to NNRTIs, and 57 of them (59.4% of patients with unsuppressed viral load, 14.0% of all patients) were also resistant to NRTIs. Patients with dual-class resistance tended to be on ART for a longer time than those with NNRTI resistance only, although the difference was not statistically significant (median time 3.4 years and IQR 2.0–5.2 versus median time 2.5 years and IQR 1.4–4.2; $P = .101$). No resistance to protease inhibitors was detected. Of the 74 patients with NNRTI resistance, 73 were resistant to EFV and NVP, and 1 was resistant to NVP only. Twenty-three patients also had cross-resistance to rilpivirine and 15 had cross-resistance to etravirine. Of the 57 patients with NRTI resistance, all were resistant to 3TC and FTC. Twelve were also resistant to ZDV and d4T, 4 to ZDV, d4T, and TDF, 4 to TDF and d4T, and 1 to TDF alone. Nineteen had cross-resistance to abacavir and 7 to didanosine. The most prevalent genotypic mutations associated with resistance to NNRTIs were K103NS, Y181C, and G190AES, and those associated with resistance to NRTIs were M184IV, T215NSFY, and M41L (Figure 3).

Finally, of the 96 patients with unsuppressed viral load, 22 (23%) did not have antiretroviral drug resistance; 16 (17%) were on functional bi-therapy of 3TC and ZDV/d4T (n = 11), 3TC and TDF (n = 4), or ZDV and EVF (n = 1); 38 (40%) were on functional monotherapy of ZDV/d4T (n = 33) or TDF (n = 5); and 18 (19%) had resistance to all of the drugs of their regimen (regimen was unknown for 2 patients).

DISCUSSION

This study in rural Cameroon showed that one fifth of patients had virologic failure after a median time on first-line ART of 29 months. This figure is 2 times higher than that required to reach the 90-90-90 treatment targets.

More precisely, 23.6% of patients had a viral load >1000 copies/mL and 18.2% had antiretroviral drug resistance. These estimations were higher than those observed in 3 district hospitals in Yaoundé in 2009–2011, where they were 13.9% and 10.4% after 24 months of ART, respectively [11]. By contrast, they were lower than in a district hospital located in a very remote area in north Cameroon in the same period 2009–2011 (38.6% and 28.9%, respectively) [16]. A pilot study performed in 2013 in 2 regions of Cameroon, which included the same region as the present study, suggested poorer performances for early warning indicators of antiretroviral drug resistance (1) in rural than in urban settings as well as (2) at the primary district level compared with secondary or tertiary level [6]. Thus, our study confirms that ART effectiveness is increasingly challenging with the remoteness in Cameroon. On the one hand, this might be due to patient-related factors such as longer distance and time to reach hospital, lower incomes, lower literacy, and poorer living conditions in rural settings. On the other hand, the lower ART effectiveness in rural settings might come from healthcare-related factors such as poorer knowledge and experience of healthcare workers in HIV/AIDS management and ART use, greater staff shortage (especially shortage of physicians and pharmacists),

Table 2. Prevalences of Unsuppressed Viral Load and Antiretroviral Drug Resistance by Time on ART

		Viral Load >1000 copies/mL			Resistance to NNRTIs			Resistance to NRTIs		
Time on ART (months)	N	n	%	95% CI	n	%	95% CI	n	%	95% CI
6–12	75	9	12.0	5.6–21.6	6	8.0	3.0–16.6	4	5.3	1.5–13.1
13–24	92	22	23.9	15.6–33.9	15	16.3	9.4–25.5	9	9.8	4.6–17.8
25–36	70	17	24.3	14.8–36.0	14	20.0	11.4–31.3	12	17.1	9.2–28.0
37–48	65	18	27.7	17.3–40.2	12	18.5	9.9–30.0	10	15.4	7.6–26.5
49–72	57	15	26.3	15.5–39.7	14	24.6	14.1–37.8	10	17.5	8.7–29.9
>72	48	15	31.3	18.7–46.3	13	27.1	15.3–41.8	12	25.0	13.6–39.6
Total	407	96	23.6	19.5–28.0	74	18.2	14.6–22.3	57	14.0	10.8–17.8

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

Table 3. Factors Associated With Unsuppressed Viral Load and Antiretroviral Drug Resistance Using Logistic Regressions

	Viral Load >1000 Copies/mL						Resistance					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	*P*	aOR	95% CI	*P*	OR	95% CI	*P*	aOR	95% CI	*P*
Gender												
Male	1.00			1.00			1.00			1.00		
Female	0.87	0.52–1.46	.601	0.92	0.51–1.63	.768	0.88	0.50–1.56	.666	0.95	0.50–1.80	.872
Age (year)												
≤35	1.00			1.00			1.00			1.00		
>35	0.68	0.41–1.10	.117	0.65	0.38–1.14	.134	0.77	0.45–1.33	.358	0.65	0.35–1.20	.168
School educational level												
Less than secondary	1.00						1.00					
Secondary or higher	1.25	0.72–2.14	.429				1.28	0.71–2.34	.413			
Marital status												
Single or divorced	1.00						1.00					
Married or cohabiting	0.88	0.54–1.45	.615				0.90	0.52–1.55	.700			
Widowed	0.49	0.20–1.15	.101				0.58	0.23–1.45	.241			
Bodyweight (per 1-kg increase)	0.98	0.96–1.00	.085				0.98	0.96–1.01	.124			
WHO stage												
1 or 2	1.00						1.00					
3 or 4	1.44	0.76–2.71	.260				1.84	0.87–3.89	.111			
CD4 cell count (cells/μL)												
<100	1.00			1.00			1.00			1.00		
≥100	0.53	0.31–0.89	.018	0.58	0.34–0.99	.047	0.47	0.27–0.83	.009	0.52	0.29–0.94	.029
Hemoglobin (g/dL)												
<8	1.00						1.00					
8–10	0.63	0.28–1.39	.248				0.61	0.26–1.42	.248			
11–13	0.45	0.19–1.07	.072				0.50	0.20–1.25	.138			
≥14	0.83	0.23–2.97	.778				0.57	0.13–2.47	.454			
Time on ART (per 1-year increase)	1.13	1.01–1.27	.032	1.17	1.01–1.34	.033	1.19	1.05-1.34	.006	1.23	1.05–1.43	.009

Abbreviations: aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; NRTI, nucleoside reverse-transcriptase inhibitor; WHO, World Health Organization.

poorer laboratory infrastructures (to monitor ART effectiveness and adverse events), and higher frequency of drug stock-outs. However, it is worth noting that a previous study in Cameroon reported a better adherence to ART among patients followed up in rural district hospitals than among those followed up in major hospitals in Yaoundé and Douala [17].

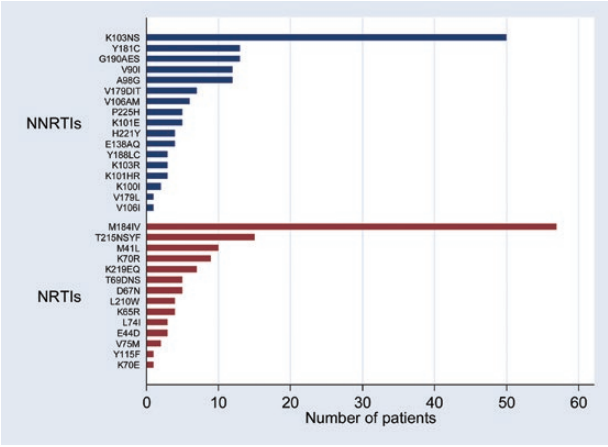

Figure 3. Genotypic nucleoside reverse-transcriptase inhibitor (NRTI) and non-NRTI-associated resistance mutations.

Compared with other west and central African countries, our estimations were among the highest [11, 18–20]. It is of interest to note that our estimations were comparable to those found in rural Togo, but, in contrast to Cameroon, virologic failure tended to be comparable between rural and urban areas in this country [11, 21]. In rural Gabon, a very high proportion of patients (41.3%) had a viral load >1000 copies/mL, and 21.3% had resistance after a median time on ART of 34 months [22]. It is important to note that discrepancies between our estimations and previous results could not be explained by differences in ART monitoring because all studies were performed among patients followed up without routine viral loads.

The prevalences of unsuppressed viral load and antiretroviral drug resistance were comparable between women and men, in accordance with some studies [22, 23] including 1 in Yaoundé [10]. By contrast, men were more vulnerable to virologic failure than women in other studies [18, 24–26]. One of these studies was performed in 9 district hospitals (including the Mfou one) in the same region of Cameroon as the present

study [27]. The reason for the discrepancy between both studies is unclear.

The profile of genotypic resistances among patients receiving first-line ART was as expected [28, 29]. All patients with antiretroviral drug resistance were resistant to NNRTIs, and three quarters of them were also resistant to NRTIs. The fixed-dose combination of d4T, 3TC, and NVP has been extensively used in the first years of the Cameroonian programme [30]. In 2010, all patients on d4T were switched to ZDV or TDF. From 2010 to 2014, the first choice was ZDV, 3TC, and NVP/EFV, whereas TDF was mostly prescribed for patients with anemia or those infected with hepatitis B virus. The TDF-based regimen became the first choice thereafter [5]. In the absence of routine resistance testing, patients with first-line ART failure are switched to second-line regimen including TDF if first-line treatment incorporated ZDV (and vice versa), 3TC, and boosted atazanavir or lopinavir. None of our patients had resistance to protease inhibitors. By contrast, 4 patients were resistant to both TDF and ZDV. Such patients in routine care therefore receive a functional monotherapy of boosted protease inhibitor, and second-line ART could be less efficient.

It is important to note that approximately 20% of patients were susceptible to transmit resistant HIV because they had high viral loads and antiretroviral drug resistances. In the absence of resistance testing at ART initiation, patients infected with resistant HIV receive a standard first-line treatment and are likely to add to those with unsuppressed viral load. Regarding the 22 patients with unsuppressed viral load but without resistance, their median viral load suggests that they might have shorter failure time than patients with resistance.

Our findings should be interpreted taking into account several study limitations. First, we did not perform a second measurement of viral load 3 months apart, with adherence support, as recommended by the WHO to define virologic failure. However, we performed resistance testing among patients with viral load >1000 copies/mL. The prevalence of virologic failure as defined by the WHO was therefore between 18.2% (proportion of patients with resistance) and 23.6% (proportion of patients with a single viral load >1000 copies/mL). Second, our estimations of prevalence should be seen as a minimum at the programme level because of the cross-sectional design, the subsequent exclusion of patients who were deceased (probably because of therapeutic failure) or transferred-out (for instance to Yaoundé for getting second-line ART), and the relatively low proportion of eligible patients who were included (58.0%). Unreachable patients who predominated among eligible but not included patients could either be followed up in other clinics or have stopped ART.

CONCLUSIONS

In conclusion, the proportion of patients with virologic failure should be divided at least by 2 to reach the UNAIDS 90-90-90 treatment targets. Strengthening the health system capacities through HIV and ART-specific training of healthcare workers, laboratory equipments, and adequate drug supply is important, especially in the rural setting. In addition, the surveillance of virologic failure and resistance will be crucial to preserve future treatment options.

Acknowledgments

We thank all the patients and staff of the Mfou District Hospital who participated in the study.

Financial support. The study was supported by grants from Institut de Recherche pour le Développement (LMI PreVIHMI) and Ensemble pour une Solidarité Thérapeutique Hospitalière En Réseau.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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